REMARKS

It is respectfully requested that the amendments presented in the previous section be entered pursuant to the provisions of 37 C.F.R. §1.116(b); that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining in this application be allowed.

Claim Amendments

Claims 27, 28-45, 53 and 54 are amended herein.

Claims 52 and 56 are canceled. Accordingly, Claims 27-51 and 53-55 are currently pending in the application.

The amendments made herein are requested solely to expedite the prosecution of what is believed to be allowable subject matter. Applications specifically reserve the right to file one or more continuation/divisional applications directed to the subject matter therein.

Claims 28-46 were amended to revert to the original numbering consistent with the amendment originally filed on January 16, 2003. It appears that applicants' attorney, in Appendix B of the later amendment dated May 3, 2004, inadvertently mis-numbered the claims by (i) deleting the numerical indicator on claim 28 and (ii) presenting duplicates of Claim 47 (as claims 46 and 47). Applicants' undersigned attorney recognizes the prohibition against re-numbering claims, but respectfully submits that this submission is not, strictly speaking, a re-numbering, since (i) the amended form of the claims in the later amendment did not show the error (it was only in the "clean" version), and (ii) the Examiner apparently recognized the error and subsequently referred to the claims using the correct reference numbers. Nonetheless, for avoidance of doubt, applicants herein present the claims in "amended" form.

Claim 27 has been amended to bring out the feature that the claimed compound is one having a binding affinity to VLA-4 characterized by an IC_{50} of 15μM or less, as determined using competitive binding assay. Support for this feature of the invention is provided, for

example, in Example A of the specification, which exemplifies a standard type of competitive binding assay known in the art.

Claim 27 has also been amended to correct several typographical and formatting errors; all amendments are presented in boldface, to facilitate review:

In the description of the substituent R^{2a}, specifically sub-paragraph (i) thereof, wherein R^{2a} is (i) Ar^1R^9, at S^1 (acylamino), the final paragraph has been numbered "(16)" to indicate a separate substituent,

Further in the description of the substituent R^{2a}, sub-paragraph (ii) thereof in the description of the group B, at (L^2), the term "-So_n-" has been corrected to "-SO_n-."

Also in the description of the group B, at (Q^2), the term "heteroayl" has been corrected to read "heteroaryl."

Also in the description of the substituent B, also in the description of heteroaryl at (Q^2), the terms "substituted heterocyclic" and substituted alkynyl groups," previously in paragraph (h), have been split into paragraphs (h) and (i), respectively to bring out the feature that these are, in fact, distinct substituents.

Further in the description of the group B, previous sub-paragraphs (R^2) to (H^3) have been re-numbered as (32)-(48) to indicate their proper hierarchy under sub-paragraph (Q^2). Support for this feature of the invention can be found, for example, in the specification at page 8 line 22 to page 9 line 13 thereof, as amended by way of the Amendment dated August 7, 2002.

In the description of group C, also under substituents R^{2a}, in sub-paragraph (U^3), the term "-So_n-" has been corrected to read "SO_n".

Further under the description of group C, sub-paragraph (Z^3) has been re-punctuated to bring out the delineation of the description of the bi or tri-fused ring system at the end of the description.

Claim 27 has been further amended to add descriptions of the substituents R^3, R^{3a}, R^{16}, R^{18} and R^{20}, as shown in the structural depiction of Formula I. Support for these amendments can be found, for example in Claim 1 as originally presented. The various recited substituents

have further been defined with reference to the descriptions throughout the specification, as previously amended into Claim 27. Applicants note that one additional definition has been incorporated into the description of the substituents "substituted amino" at sub-paragraph Q^5 of the description of R^{16}. Support for this definition is found, for example, in the specification, at page 39, lines 10-20 thereof.

Claim 28 has been amended to remove redundant reference to Claim 27, on which it depends.

Claim 31 has been amended to correct the second subscript to **11'** (from 11) in the term "-OC(O)$NR^{11}R^{11'}$-."

Claim 38 has been amended to remove reference to R^2 and R^3, which are not present in the formula of the claimed compound.

Claim 40 has been amended to remove the word "the" from the fourth line of the claim.

Claim 41 has been amended to remove the word "preferably" from the language of the claim, in conformance with standard claiming practice.

Claim 53 has been amended to depend from Claim 27.

Claim 54 has been amended to recite specific VLA-4-mediated diseases.

Applicants submit that no new matter has been entered by the foregoing amendments to the claims.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 27-52 were rejected on the grounds that they are allegedly indefinite. The Examiner's comments and the steps and/or arguments to overcome them are presented below.

(i) Theaminer asserted that the method of measuring binding affinity to VLA-4 should be incorporated into Claim 27. By this amendment, claim 27 has been amended to recite that the

binding affinity to VLA-4 is determined using a competitive binding assay. Such an assay is described by way of example in Example A of the specification. Accordingly, applicants respectfully submit that they have overcome the Examiner's objections with regard to independent Claim 27 and Claims 28-51 and 52-55, dependent thereon.

(ii) The Examiner further asserts that it is unclear in Claim 54 which diseases are mediated by VLA-4. Claim 54 has been amended to recites a number of specific disorders in which VLA-4 integrin interactions are involved, as supported in the specification. This list of disorders is the same as is recited in previously amended Claim 50.

(iii) The Examiner questions the intent of Claims 52 and 56. While the applicants believe that each of these claims has utility, in order to expedite prosecution, Claims 52 and 56 are canceled by this amendment.

(iv)-(vii) The Examiner believes that the terms "cycloalkyl," "heteroaryl," "heterocyclic," and "substituted" are indefinite. By this amendment, Claim 53 amended to depend from Claim 27, which includes definitions for these terms, along the lines previously required by the Examiner.

Rejections under 35 U.S.C. §112, first paragraph.

(i) Claims 48, 50, 54 and 56 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification, while being enabling for treating asthma, does not enable any and all diseases embraced by the claims.

Claim 56 stands canceled by this amendment, as stated above. Accordingly, in the sections that follow, applicants will address this rejection with regard to the remaining claims (48, 50 and 54).

Claims 48, 50 and 54 are all directed to methods of treating specific diseases mediated by VLA-4. The claims are distinct, one from another, by virtue of the compounds they recite. It is

the Examiner's position that the specification does not enable all the diseases listed. Applicants respectfully traverse this rejection for the reasons that follow:

The test of enablement is whether the applicants' disclosure teaches how to make and use the invention as claimed.

As a matter of Patent Office practice... a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

The claimed invention encompasses certain VLA-4-inhibitory compounds that are used to treat specific inflammatory conditions, namely those conditions in which a specific integrin, $\alpha_4\beta_1$ (VLA-4) is involved. Applicants have provided information in the specification, for example at page 3, lines 21 to 30 supporting the fact that VLA-4 is involved in conditions characterized by inappropriate or heightened inflammatory responses associated with leucocyte-endothelial cell destruction of otherwise healthy tissue. Further support for this concept, as well as a listing of the diseases most closely associated with such responses can be found, for example, at page 4, lines 1 to 23. Additional rationale for such conditons is provided, for example, at page 94, line 1 to page 95, line 22.

The applicants describe how to make the specific VLA-4-inhibitory compounds in sufficient detail so that persons skilled in the art can reliably produce such compounds. Synthetic details are provided in the specification, for example, at page 57, line 1 to page 79, line 18; detailed synthetic routes are also provided in the Examples. Criteria for selecting active compounds are provided by way of exemplary assays, both *in vitro* and *in vivo*, that guide the practitioner to choose compounds having requisite VLA-4-inhibitory activity, for example, in Examples A-D, starting on page 102 of the specification. The applicants further describe

appropriate formulations for the use of such compounds in pharmaceutical formulations, for example at page 79, line 20 to page 83, line 2, and by specific example at page 83, line 7 to page 88, line 12. Guidelines for dosing mammalian subjects are found, for example at page 96, line 29 to page 97, line 8.

Thus, the instant specification provides specific guidance on how to make and identify active compounds, how to formulate such compounds into pharmaceutical compositions, and have provided dosing guidelines for administering compounds to patients. In addition, the applicants have provided a clear description of specific VLA-4 mediated disorders in which these compounds can be used, supported by credible rationale based on scientific principles and example.

Furthermore, applicants submit that they have provided ample evidence to support the fundamental nature of their invention, which provides pharmaceutical means to interfere with a basic mechanism underlying a number of otherwise disparate inflammatory conditions. Accordingly, applicants submit that the teachings of the specification provide ample support for making and using the invention in terms corresponding in scope to the invention as claimed.

Since the Examiner has provided no objective reason to doubt the applicants' teachings in this regard, applicants respectfully submit the disclosure is in compliance with the requirements of 35 U.S.C. §112, first paragraph. Accordingly, withdrawal of the rejections under this section is respectfully requested.

(ii) Claims 52 and 56 were rejected under U.S.C. §112, first paragraph on the grounds that the specification fails to teach any benefit to be gained from binding VLA-4 *in vitro*. While applicants do not agree with either the premise or the basis for this rejection, by this amendment, Claims 52 and 56 stand canceled, without prejudice.

In view of the foregoing, applicants submit that the claims, as currently amended, are in compliance with the requirements of 35 U.S.C. 112. Accordingly, withdrawal of the rejections under this section is respectfully requested.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: April 16, 2004

By _____

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